claim 1 so that expression of human cholesteryl ester transfer protein is inhibited.

REMARKS

Claims 1, 2 and 4-20 are pending in the instant application. Claims 1, 2 and 4-20 have been rejected. Claims 11 and 16-20 have been canceled. Claims 1 and 15 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claim 1 has been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner suggests that this claim is drawn to a compound which hybridizes with an active site which is not defined in a way in the specification that allows one to understand how it is experimentally determined. Applicants have canceled claim 11. Therefore, withdrawal of this rejection is respectfully requested.

Claims 15-20 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification while being enabling for antisense inhibition of human cholesteryl ester transfer protein expression *in vitro* does not reasonably provide enablement for *in vivo* antisense inhibition of expression of cholesteryl ester transfer protein; the Examiner cites several articles to support this position. Applicants respectfully traverse this rejection of the claims.

Applicants disagree with the Examiner's suggestion that cited references support the position that application of antisense *in vivo* is highly unpredictable.

The Examiner has pointed to articles concerning the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of the papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis

to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans. Therefore, what these papers cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals and humans. Nowhere in the references cited do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

The paper by Braasch and Corey (2002) describes the advances that have been made in the design of antisense compounds over the years. Included in the discussion are the types of advances that are taught in the specification as filed. Nowhere in the reference do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*. In fact, the paper states in the abstract that success in clinical trials with these agents has occurred.

The paper by Tamm et al. (2001) is another more recent review of the antisense technology and its specific application to oncology. Again, although the use of antisense is discussed in terms of what can go wrong, the paper again describes advances such

as those taught in the instant specification. Nowhere in the reference do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

The paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The papers by Gewirtz et al. (1996) and Agrawal (1996) are older papers not relevant to the state of the art of antisense compounds in 2001, the filing date of the instant application. Both papers discuss in general terms issues that were related to older antisense technology. However, nowhere do these papers state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

However, Applicants have amended claim 15 and canceled claims 16-20 in an earnest effort to advance the prosecution. Applicants reserve the right to file a continuing application directed to this subject matter without prejudice. Withdrawal of the rejection is requested in light of these amendments.

II. Rejection of Claims Under 35 U.S.C. 102(b)

Claims 1, 2, 4 and 5 have been rejected under 35 U.S.C. 102(b) as being anticipated by Liu et al. (1999). The Examiner suggests that this paper discloses an antisense compound with phosphorothioate modifications that hybridize with and inhibit expression of human cholesteryl ester transfer protein. Applicants respectfully traverse this rejection.

At the outset, Applicants have amended claim 1, and by dependency claims 2-15, to refer to antisense compounds targeted to specific regions of a CETP nucleic acid molecule specified by SEQ ID NO. Support for these amendments can be found throughout the specification as filed but in particular at pages 99-102.

Liu et al. (1999) disclose a single antisense oligonucleotide targeted to positions 329-349 of the human CETP sequence of Drayna (1987). Nowhere does this patent teach or suggest antisense compounds from 15 to 50 nucleobases in length that target specific regions of the CETP nucleic acid molecule of SEQ ID NO: 3 as claimed. In order to anticipate a claim, the reference cited must teach each and every limitation of the claims (MPEP 2131). Accordingly, this patent fails to teach the limitations of the claims and cannot anticipate the instant invention. Withdrawal of this rejection is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2 and 4-14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al., or Drayna et al., in view of Baracchini et al. The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill to incorporate modifications as taught by Baracchini et al. into the antisense of Liu et al. or antisense designed from the complementary sequence of Drayna et al., because Baracchini teach the desirability of such modifications. The Examiner suggests one of skill would have been motivated to create such compounds due to the teaching of Liu et al. and Drayna et al. regarding the significant of this protein in disease. The Examiner suggests one of skill would have had an expectation of success based on the teachings of Liu et al. and Baracchini et al. Applicants respectfully traverse this rejection.

At the outset, claim 1 and its dependent claims have been amended as discussed *supra* to recite antisense compounds targeted to specific regions of a nucleic acid molecules encoding CETP of SEQ ID NO: 3.

As discussed supra, Liu et al. disclose only a single antisense compound that is targeted to a specific area of the nucleic acid sequence of Drayna et al. Nowhere does this reference teach or suggest antisense compounds targeted to CETP nucleic acid

molecules as claimed, including specific regions of CETP of SEQ ID NO: 3. Therefore, this primary reference fails to teach the limitations of the claims.

Drayna et al. (1987) discloses the sequence of human CETP. Nowhere does this reference teach or suggest antisense compounds of any type targeted to CETP nucleic acid molecules as now claimed, including specific regions of CETP. Therefore, this primary reference also fails to teach the limitations of the claims.

The secondary reference cited fails to overcome the deficiencies in teaching of the primary references.

Baracchini et al. (US Patent 5,801,154) teaches methods of modifying antisense oligonucleotides to enhance activity. However, nowhere do this patent teach or suggest antisense oligonucleotides 8 to 50 nucleobases in length targeted to CETP nucleic acid molecules, or any region of a CETP nucleic acid molecule.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations.

Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims as amended, which claim antisense compounds targeted to specific regions of a nucleic acid molecule encoding CETP, and thus cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 11 and 16-20 have been canceled without prejudice.

The claims have been amended as follows:

1. (amended) A compound 8 to 50 nucleobases in length targeted to a 5'-untranslated region, a start codon region, nucleobases 161 through 170, nucleobases 201 through 220, nucleobases 311 through 328, nucleobases 351 through 370, nucleobases 446 through 465, nucleobases 641 through 660, nucleobases 711 through 730, nucleobases 771 through 790, nucleobases 799 through 818, nucleobases 1041 through 1060, nucleobases 1061 through 1080, nucleobases 1411 through 1430, or nucleobases 1571 through 1590 of a coding region, a stop codon region, or a 3'-untranslated region of a nucleic acid molecule encoding human cholesteryl ester transfer protein (SEQ ID NO: 3), wherein said compound specifically hybridizes with ~~a nucleic acid molecule encoding human cholesteryl ester transfer protein~~ one of said regions and inhibits the expression of human cholesteryl ester transfer protein.

15. (amended) A method of inhibiting the expression of human cholesteryl ester transfer protein in cells or tissues comprising contacting said cells or tissues *in vitro* with the compound of claim 1 so that expression of human cholesteryl ester transfer protein is inhibited.